

CLAIMS

1. A method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:

determining a level and/or an activity of

- (i) a transcription product of a gene coding for a vault protein, and/or
- (ii) a translation product of a gene coding for a vault protein and/or
- (iii) a fragment, or derivative, or variant of said transcription or translation product in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

2. A method of monitoring the progression of a neurodegenerative disease in a subject, comprising:

determining a level and/or an activity of

- (i) a transcription product of a gene coding for a vault protein, and/or
- (ii) a translation product of a gene coding for a vault protein, and/or
- (iii) a fragment, or derivative, or variant of said transcription or translation product in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby monitoring the progression of said neurodegenerative disease in said subject.

3. A method of evaluating a treatment for a neurodegenerative disease, comprising:

determining a level and/or an activity of

- (i) a transcription product of a gene coding for a vault protein, and/or
- (ii) a translation product of a gene coding for a vault protein, and/or
- (iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample from a subject being treated for said disease and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby evaluating said treatment for said neurodegenerative disease.

4. The method according to any of claims 1 to 3 wherein said neurodegenerative disease is Alzheimer's disease.

5. The method according to any of claims 1 to 4 wherein said vault protein is a minor vault protein, in particular the minor vault protein ADPRTL1.

6. The method according to any of claims 1 to 5 wherein said sample comprises a cell, or a tissue, or a body fluid, in particular cerebrospinal fluid or blood.

7. The method according to any of claims 1 to 6 wherein said reference value is that of a level and/or an activity of

- (i) a transcription product of a gene coding for a vault protein, and/or
- (ii) a translation product of a gene coding for a vault protein, and/or
- (iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample from a subject not suffering from said neurodegenerative disease.

8. The method according to any of claims 1 to 7 wherein an alteration in the level and/or activity of a transcription product of the gene coding for the minor vault protein ADPRTL1 and/or a translation product of a gene coding for the minor vault protein ADPRTL1, and/or a fragment, or derivative, or variant thereof, in a sample cell, or tissue, or body fluid, in particular cerebrospinal fluid, from said subject relative to a reference value representing a known health status indicates a diagnosis, or prognosis, or increased risk of Alzheimer's disease in said subject.

9. A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a disease, said kit comprising:

- (a) at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of a gene coding for a vault protein and (ii) reagents that selectively detect a translation product of a gene coding for a vault protein and
- (b) an instruction for diagnosing, or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of a subject to develop such a disease by (i) detecting a level, or an activity, or both said level and said activity, of said transcription product and/or said

translation product of a gene coding for a vault protein, in a sample from said subject; and (ii) diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of said subject to develop such a disease, wherein a varied level, or activity, or both said level and said activity, of said transcription product and/or said translation product compared to a reference value representing a known health status; or a level, or activity, or both said level and said activity, of said transcription product and/or said translation product similar or equal to a reference value representing a known disease status indicates a diagnosis or prognosis of a neurodegenerative disease, in particular Alzheimer's disease, or an increased propensity or predisposition of developing such a disease.

10. A method of treating or preventing a neurodegenerative disease, in particular AD, in a subject comprising administering to said subject in a therapeutically or prophylactically effective amount an agent or agents which directly or indirectly affect an activity and/or a level of

- (i) a gene coding for a vault protein, and/or
- (ii) a transcription product of a gene coding for a vault protein, and/or
- (iii) a translation product of a gene coding for a vault protein, and/or
- (iv) a fragment, or derivative, or variant of (i) to (iii).

11. A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

- (i) a gene coding for a vault protein and/or
- (ii) a transcription product of a gene coding for a vault protein and/or
- (iii) a translation product of a gene coding for a vault protein, and/or
- (iv) a fragment, or derivative, or variant of (i) to (iii).

12. A recombinant, non-human animal comprising a non-native gene sequence coding for a vault protein or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:

- (i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and
- (ii) introducing said targeting construct into a stem cell of a non-human animal, and
- (iii) introducing said non-human animal stem cell into a non-human embryo, and

- (iv) transplanting said embryo into a pseudopregnant non-human animal, and
- (v) allowing said embryo to develop to term, and
- (vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and
- (vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

13. The animal according to claim 12 wherein said vault protein is a minor vault protein, in particular the minor vault protein ADPRTL1, SEQ ID NO.2.

14. Use of the recombinant, non-human animal according to claim 12 or 13 for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

15. An assay for screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

- (i) a gene coding for a vault protein, and/or
 - (ii) a transcription product of a gene coding for a vault protein, and/or
 - (iii) a translation product of a gene coding for a vault protein, and/or
 - (iv) a fragment, or derivative, or variant of (i) to (iii),
- said method comprising:
- (a) contacting a cell with a test compound;
 - (b) measuring the activity and/or level of one or more substances recited in (i) to (iv);
 - (c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and
 - (d) comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

16. A method of screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

- (i) a gene coding for a vault protein, and/or
- (ii) a transcription product of a gene coding for a vault protein, and/or
- (iii) a translation product of a gene coding for a vault protein, and/or
- (v) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

- (a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);
- (b) measuring the activity and/or level of one or more substances recited in (i) to (iv);
- (c) measuring the activity and/or level of one or more substances recited in (i) or (iv) in a matched control animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect to the substances recited in (i) to (iv) and to which animal no such test compound has been administered;
- (d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the test animal indicates that the test compound is a modulator of said diseases or disorders.

17. The method according to claim 16 wherein said test animal and/or said control animal is a recombinant animal which expresses a vault protein, or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native vault protein gene transcriptional control element.

18. An assay for testing a compound, preferably for screening a plurality of compounds for inhibition of binding between a ligand and a vault protein, or a fragment, or derivative, or a variant thereof, said assay comprising the steps of:

- (i) adding a liquid suspension of said vault protein, or a fragment, or a derivative, or a variant thereof, to a plurality of containers;
- (ii) adding a compound, preferably a plurality of compounds, to be screened for said inhibition of binding to said plurality of containers;

- (iii) adding a detectable ligand, in particular a fluorescently detectable ligand, to said containers;
- (iv) incubating the liquid suspension of said vault protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds, and said ligand;
- (v) measuring amounts of detectable ligand or fluorescence associated with said vault protein, or with said fragment, or derivative, or variant thereof; and
- (vi) determining the degree of inhibition by one or more of said compounds of binding of said ligand to said vault protein, or said fragment, or derivative, or variant thereof.

19. An assay for testing a compound, preferably for screening a plurality of compounds to determine the degree of binding of said compounds to a vault protein, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:

- (i) adding a liquid suspension of said vault protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;
- (ii) adding a detectable compound, preferably a plurality of detectable compounds, in particular fluorescently detectable compounds, to be screened for said binding to said plurality of containers;
- (iii) incubating the liquid suspension of said vault protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds;
- (iv) measuring amounts of detectable compound or fluorescence associated with said vault protein, or with said fragment, or derivative, or variant thereof; and
- (v) determining the degree of binding by one or more of said compounds to said vault protein, or said fragment, or derivative, or variant thereof.

20. A protein molecule, said protein molecule being a translation product of the gene coding for a vault protein, in particular the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, for use as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.

21. A protein molecule, said protein molecule being a translation product of the gene coding for a vault protein, in particular the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, for use as a screening

target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

22. Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for a vault protein, in particular the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, for detecting the pathological state of a cell in a sample from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell, and wherein said pathological state relates to a neurodegenerative disease, in particular Alzheimer's disease.